Committee, Public and Projector slides

Chair's Presentation Mepolizumab for treating severe refractory eosinophilic asthma

3rd Appraisal committee meeting

Committee B, October 2016

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Company: GSK

NICE team: Wendy Gidman, Jasdeep Hayre, Helen Tucker, Raisa Sidhu

Evidence Review Group: School of Health and Related Research (ScHARR), The University of Sheffield

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Issues for discussion

1. Population: appropriate?
2. Comparator: Has the committee heard anything to change its decision on omalizumab as a comparator?
3. Modelling: Is company's duration of an 'exacerbation' valid?
4. Utility: Does mepolizumab increase HRQoL over and above reducing exacerbations?
5. Is company's choice of way to adjust baseline EQ-5D appropriate?
6. How should utility be adjusted by age, using company data, or in line with ACD2 consideration?
7. Should age at starting mepolizumab be lower and reflect the NHS?
8. What is the appropriate criteria for continuing treatment and how does this affect utility?

History of this appraisal

1st meeting March 2016
ACD1 issued: **Mepolizumab not recommended**

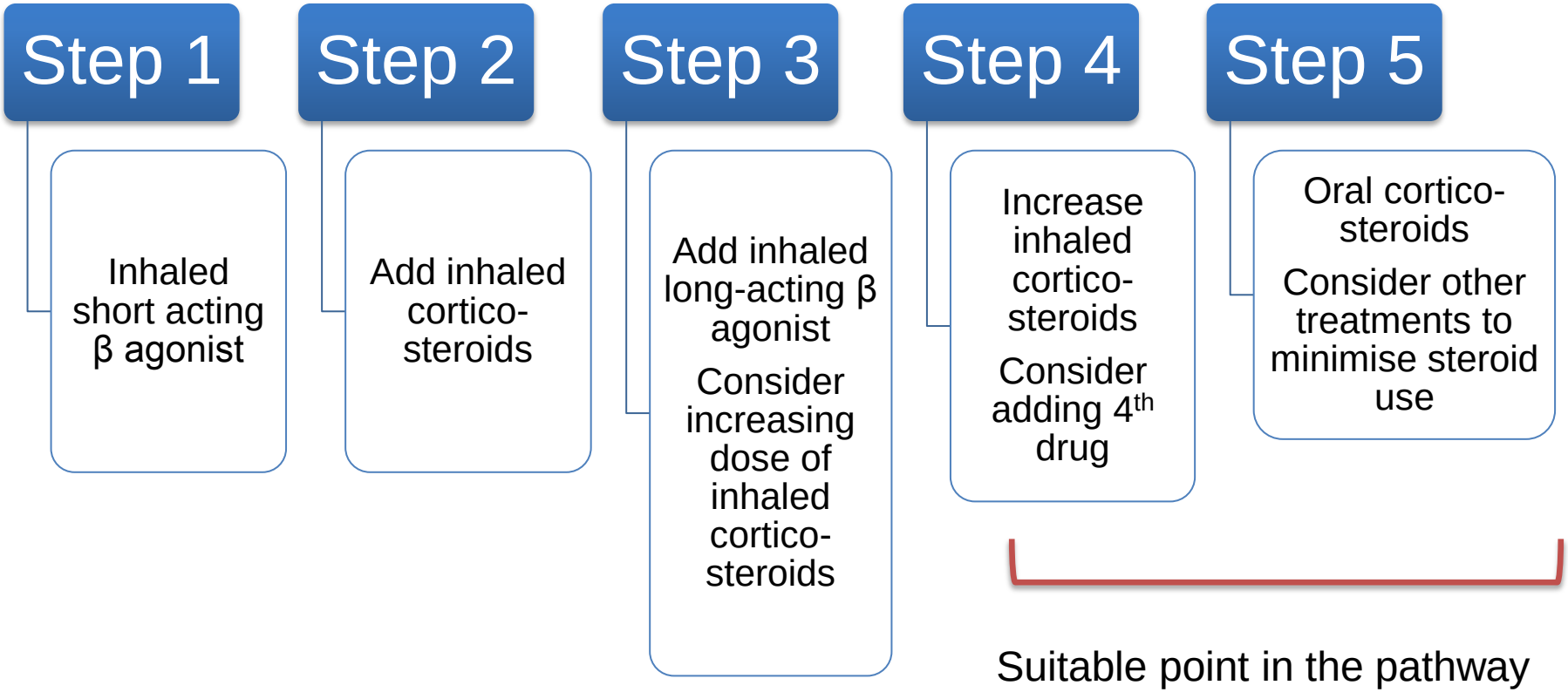
2nd meeting May 2016
New evidence: populations, additional scenario analyses
ACD 2 issued: **Mepolizumab not recommended**

3rd meeting TODAY
Revised analyses: EQ-5D baseline adjusted, EQ-5D utilities on/off treatment, continuation criteria
New PAS

Mepolizumab (Nucala)

Marketing authorisation	**Add-on** treatment for severe refractory **eosinophilic** asthma in adult patient
Mode of action	Monoclonal antibody to interleukin-5
Route of delivery	100 mg fixed-dose 4-weekly subcutaneous injection
Treatment duration	Intended for 'long-term treatment' summary of product characteristics: evaluate 'at least annually'
Patient access scheme	Confidential simple discount proposed at 1st meeting and increased for this 3rd meeting

The treatment pathway
British Thoracic Society / SIGN



Suitable point in the pathway based on trial evidence & clinical opinion

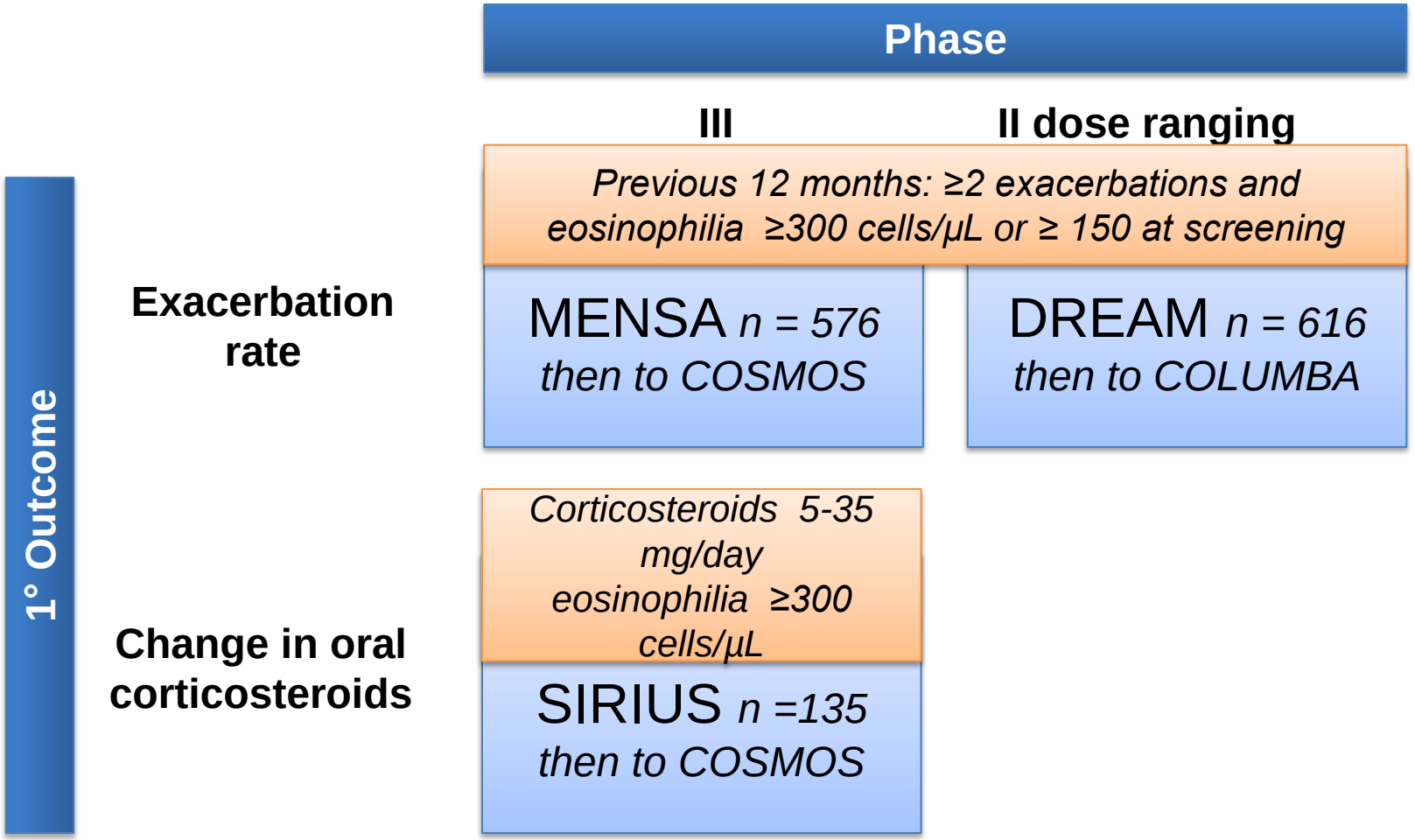
Company's 'accepted' subpopulation from trials

		Eosinophilia ≥ 300 *cells/μL and*	
		Number exacerbations in previous year	
		<4	**≥**4
Maintenance systemic corticosteroids	Yes	<4 exacerbations plus maintenance systemic corticosteroids	**≥**4 exacerbations plus maintenance systemic corticosteroids
	No	<4 exacerbations no maintenance systemic corticosteroids	**≥**4 exacerbations no maintenance systemic corticosteroids

'accepted' population

n.b. GSK's original 'proposed population' same boxes but different value for eosinophilia

Summary evidence
placebo-controlled trials & follow-on studies



- COSMOS (n=651) Open label extension to MENSA and SIRIUS, 1 year
- COLUMBA (n=347) ongoing. Patients from DREAM up to 3.5 years

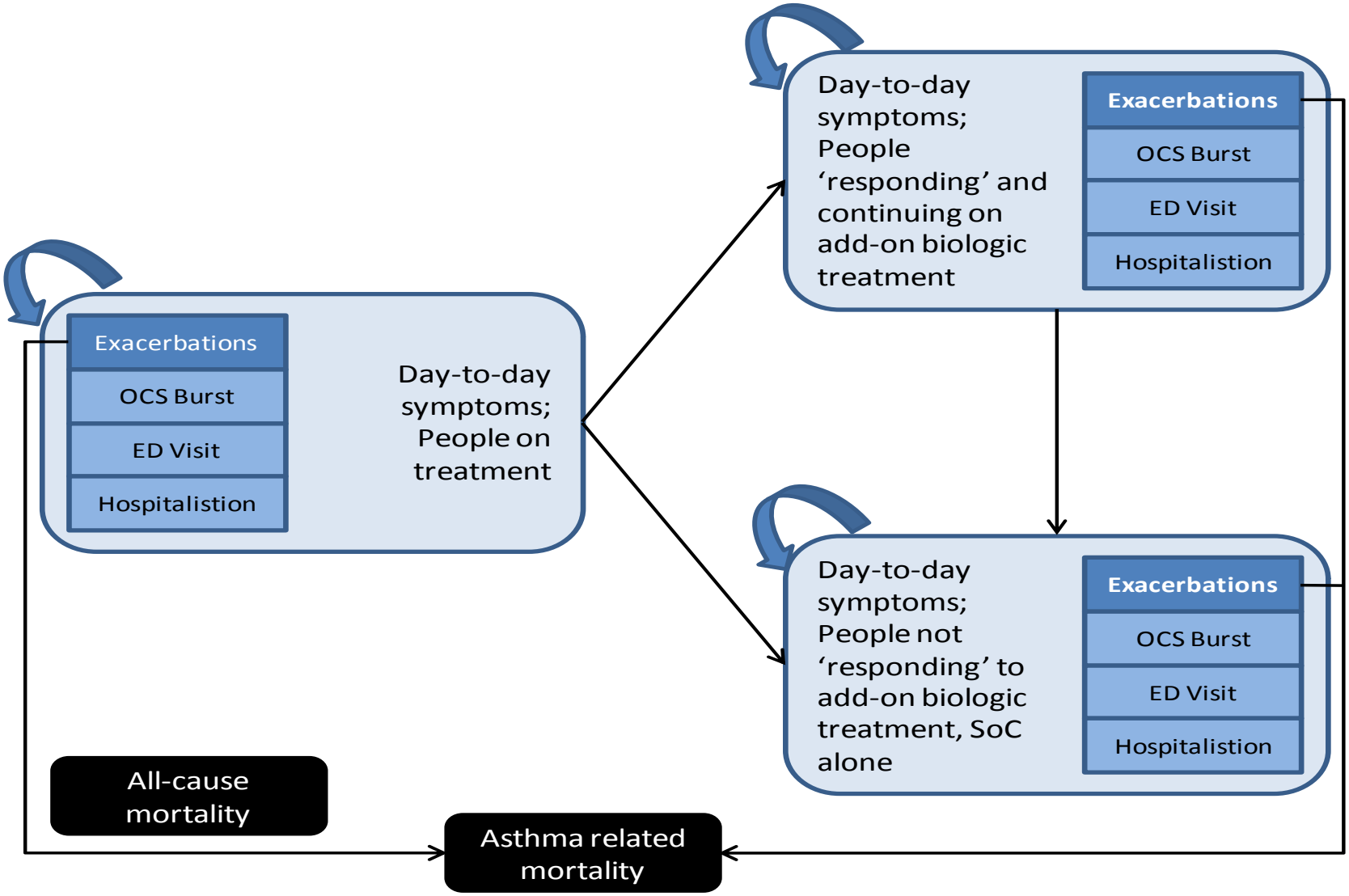
Modified intention to treat population: rate ratios for mepolizumab vs placebo

	Clinically significant exacerbations (Rate ratio 95% CI)	Exacerbations requiring hospitalisation (Rate ratio 95% CI)	Odds ratio of reducing corticosteroids (while maintaining asthma control), between weeks 20 and 24 (95% CI)
MENSA pooled 75 mg IV & 100 mg subcut	0.50 (0.39 to 0.64)	0.44 (0.19 to 1.02)	NA
DREAM 75 mg IV	0.52 (0.39 to 0.69)	0.61 (0.28 to 1.33)	NA
DREAM + MENSA 75 mg IV & 100 mg subcut	0.51 (0.42 to 0.62)	0.50 (0.28 to 0.89)	NA
SIRIUS 100 mg subcut	0.68 (0.47 to 0.99)	NA	2.39 (1.25 to 4.56)

EMA deemed recommended dose 100 mg given subcut every 4 weeks bioequivalent to 75 mg given IV every 4 weeks weeks

Modified ITT population had at least 1 dose of treatment
CI: confidence interval

Schematic of the Markov model structure



OCS:oral corticosteroid; ED: emergency department

Committee's key consideration in ACD2
Clinical considerations

Issue	Committee's consideration
Population	Clinical expert: threshold of blood eosinophil count of ≥150 cells/μL 'normal' whereas ≥300 cells/μL reflects practice Conclusion: population that best reflects UK practice: • people with a blood eosinophil count of ≥300/μL in previous year and ≥ 1 of: ➢ 4 or more exacerbations in the previous year ➢ on maintenance oral corticosteroids
Comparator	Not to consider comparison with omalizumab (sub-group in which both are used very small and evidence not robust)
Effectiveness	Mepolizumab reduces exacerbation rate vs. placebo

Committee's key consideration in ACD2
Cost effectiveness considerations

Issue	Committee's consideration
Continuation criteria	SPC: review once a year. Company's model assumes a review at 12 months; if exacerbation rates were **not worse** then continue treatment. Conclusion: Continuation criteria linked to **improvement** more appropriate
Exacerbation rates	Exacerbation rates underestimated by company – committee preferred ERG methods (using COSMOS data)
Waning of effect	Evidence uncertain. Mindful that waning increases ICER
Utility estimates	Committee preferred direct EQ5D values and age-adjusted utility. Possible double-counting of disutility associated with exacerbations → overestimate utility values for mepolizumab
Mortality	Committee preferred ERG age-related mortality
Age	Age in model higher than clinical practice; lower age ↑ ICERs
Conclusion	**ICERs above range normally considered cost-effective**

ACD2 consultation responses

- Consultees:
  - GlaxoSmithKline (mepolizumab)
  - Asthma UK
  - NHS England
  - Department of Health (no comment)

- Clinical expert (2)

- Web comments
  - 1 patient / carer
  - NHS Professional (consultant respiratory physician, also member of British Thoracic Society / Severe Asthma Network)

Clinical expert

- Clinical expert (1):
  - Need to define severe exacerbations as ‘severe exacerbations requiring a course of oral corticosteroids’
  - It is important that objective evidence of adherence/compliance is emphasised in the guidance
- Clinical expert (2):
  - Small risk of anaphylaxis but generally well tolerated
  - Patients who are highly eosinophilic (blood eosinophil count at start of treatment (>0.5 x109/L) benefit in terms of lung function (improvement in FEV1) and asthma control as well as exacerbation frequency
  - variability in the pattern of exacerbations means that it will require 12 months perspective to be sure that the drug is not working and allow the physician to be confident enough to stop treatment

NHS England

- NHS England comments:
  - Symptomatic improvements cannot be explained solely by decrease in exacerbation frequency
  - Further work is required with regards both the addition of a stopping rule and the impact of the improvement in on treatment utility gain

Asthma UK and Web comments

- Asthma UK:
  - EQ-5D misses mepolizumab's impact on severe asthma
  - NICE must account for improving the lives of carers, and the health and quality of life benefits of reducing corticosteroids
  - Mepolizumab could provide an option for people with severe eosinophilic asthma who currently have no treatment option
- Web comments:
  - Mother reported that her daughter participated in a trial: "for that 12 months of the trial she didn't have one episode of exacerbation of her asthma and finally felt that there was hope for her to have some kind of near normal life"

Note: the decrement in utility for a carer of a patient with severe asthma is not captured in the company's model

NHS Professional and Novartis

- NHS professional (also member of BTS/SAN):
  - Concept that patients who don't respond to mepolizumab are more likely to have severe disease than patients who do respond has no immunological or clinical plausibility
- Novartis (commentator):
  - Noted company's model included patients with eosinophil count of 300/µL AND continuous or frequent treatment with cortiocosteroids. Population should be clarified to:

    - Those of *continuous or frequent* (≥ 4) courses of oral corticosteroids in *the previous year*

Company's 'accepted' subpopulation from trials

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		Number exacerbations in previous year	
		<4	**≥**4
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	No	<4 exacerbations no maintenance systemic corticosteroids	**≥**4 exacerbations no maintenance systemic corticosteroids

'accepted' population

n.b. GSK's original 'proposed population' same boxes but different value for eosinophilia

Company's comments on comparators and populations

Population	Comparator	ACD2 committee consideration	Company's response	ERG response
Severe refractory eosinophilic asthma	Standard care	Appropriate population & comparator	Accepted	Accepted
Severe allergic IgE-mediated asthma	Omalizumab	Treatment based on predominant phenotype Comparison not appropriate: uncertainty in the evidence & small population	Asked committee to reconsider Mepolizumab likely to be cost-saving in all scenarios	ERG agrees insufficient evidence to recommend one treatment over another

⊙ ***Has the committee seen evidence to now consider omalizumab in the severe allergic IgE-mediated asthma population?***

Company's revised base case summary (1)

Committee's consideration in ACD2	Did the company revise the base case according to committee's preference?
Treatment duration (4.20): Lifetime not 10 years	✔ Committee's preferences
Exacerbation rates calculated per committee's preference - continuation criteria over full year	✔ Committee's preferences
Duration of exacerbation (4.23): Should be from MENSA	✖ Company & ERG believe duration will be somewhere between Lloyd and MENSA, so company propose midpoint (later slide)
Effect on symptoms (4.23): No effect obtained on top of exacerbations	✖ Company disagrees. Presents **new data** on impact on symptoms (later slide)

Company's revised base case summary (2)

Committee's consideration in ACD2	Did the company revise the base case according to committee's preference?	
Directly elicited EQ-5D preferred (4.22)	✔	**New analyses** with baseline adjusted EQ-5D values (later slide)
Age-adjusted utility (4.23)	✖	**New data** which in company's view show **no evidence** of utility being affected by age (later slide)
Age adjusted mortality (4.24): impact of age on asthma related mortality	✔	**New data** shows that there is an impact of age on asthma mortality (later slide)
Age (4.25) 50.1 years likely older than in clinical practice	✖	Not a large impact on ICER, so maintained at 50.1

Company's revised base case summary (3)

ACD2 suggestion	Did the company revise the base case according to committee's preference?	
Continuation Criteria: (4.15) • **original** • **50%** • **30%**	✔	New analyses (later slide)
Maintenance oral corticosteroid reduction benefit (4.28)	✖	Included as a separate scenario to base case (later slide)

In addition improved Patient Access Scheme

Duration of exacerbation

- **ACD 2**: “ERG suggested incorporating the average length of exacerbations measured in the MENSA trial, and the committee considered this appropriate”
- **Company**: at ACM2 both ERG and GSK proposed “that the duration could feasibly be between MENSA and Lloyd”
- **ERG response**: Acknowledged, note ICER slightly reduced

Type of exacerbation	MENSA	Lloyd	Midpoint – revised company base case
OCS burst	12.7	28	**20.3**
ED visit	10.4	28	**19.2**
Hospitalisation	20.7	28	**24.4**

⊙ ***Is company’s choice of exacerbation duration appropriate?***

OCS: oral corticosteroid; ED: emergency department

Effect of mepolizumab on symptoms

- **ACD2:** “mepolizumab was unlikely to have an effect on symptoms” and concluded that “on-treatment utility gain was inappropriate”
- **Company:** treatment increases utility by improving symptoms
  - Presented reanalyses of the MENSA ITT population of St George’s Respiratory Questionnaire (SGRQ) and asthma control questionnaire (ACQ-5) data to:
    - Adjust change in SGRQ for changes in exacerbations from baseline
    - prove that frequency of respiratory symptoms key driver of the change in SGRQ score
  - Other outcomes in trials show statistically significant improvement in asthma-related quality of life in trials
- **ERG:** agrees, but indicates that in new analysis, the frequency of exacerbations confounds these results

⊙ ***Does mepolizumab provide increased HRQoL over and above exacerbation reduction?***

EQ-5D used in preference to SGRQ (1)

- **ACD2:** health-related quality-of-life gain associated with mepolizumab likely overestimated in model as data had been mapped from SGRQ data. ACD2 requested direct EQ-5D data
- **Company:** EQ-5D data from DREAM had different subgroup baseline values. Company used baseline adjusted EQ-5D data differences – but acknowledged EQ-5D subgroup data counter intuitive
  - EQ5D of Standard of Care lower < ITT population, but the accepted group may have more severe disease

	Baseline EQ-5D score	End of trial (used in revised model)	
		Unadjusted EQ-5D score	Adjusted EQ-5D score
Standard Care	0.794	0.792	0.765
Mepolizumab	0.716	0.797	0.804
Difference between mepolizumab and Standard Care	-0.078	0.005	0.039

EQ-5D used in preference to SGRQ (2)

- **Company:** SGRQ does have some relevance to quantify the ceiling effect in EQ-5D and present sensitivity analysis → 'most plausible ICER' between the baseline-adjusted direct EQ-5D and the mapped EQ-5D ICERs
- **ERG:** ERG would have expected that patients in the accepted population, would have a lower mean EQ-5D score at baseline than the overall modified intention to treat population
- ERG explored the impact of removing the baseline imbalance between subgroups in its exploratory analysis

⊙ ***Is the company's baseline adjustment for EQ-5D appropriate?***

Age adjust utility and mortality

- **Age adjusted utility: ACD2**: Age adjusted utility preferred
- **Company**: reject on basis that EQ-5D data from DREAM trial stratified by age
- **ERG**: The DREAM trial was not powered to detect age-dependent utility reduction
  - NICE DSU TSD12 states that baseline utility should be age adjusted
- **Age adjusted mortality**: **ACD2**: Age impacts asthma mortality
- **Company**: Provides data from an observational study mortality by age (not in line with ACD2 consideration)
- **ERG**: Satisfied with methods, but noted that more accurate estimate could be provided with smaller ranges, noted that if mortality increases after 65 years, company's assumptions is favourable to mepolizumab

⊙ ***How should utility be adjusted by age, using company data, or in line with ACD2 consideration?***

Company proposed continuation criteria /stopping criteria

- **ACD2:** Continuation criteria linked to improvement
- **Company:** proposed mepolizumab therapy should be continued if at 12 months from starting treatment :
  - A 50% (or 30%) reduction in number of exacerbations compared to prior 12 months (50% suggested by severe asthma clinicians, or 30% aligned to a 'clinically meaningful reduction')

  OR
  - Maintenance oral corticosteroid dose falls while maintaining asthma control
    - Lowers QALY by £4,000-£9,000/QALY reduction (TA278)
- **ERG:** Cannot estimate ICER for the maintenance oral corticosteroids population because MENSA did not allow reducing maintenance oral corticosteroids dose
  - Reducing oral corticosteroids likely to affect exacerbation rates, which are main drivers of the ICER

Note: during the factual accuracy check, company queried ERG's assumptions about the continuation criteria

Company proposed continuation/stopping criteria

- **ERG:** Utility should take into account that people who discontinue will likely have more severe disease
- ERG adjusted utilities: EQ-5D utilities for patients in different states in the mepolizumab arm

Criteria for Continuation	Patients meeting criteria (%)	EQ-5D scores			
		All patients	Patients meeting criteria	Patients not meeting criteria	Mepolizumab discontinuers
Original : no worsening of exacerbations	89.9	0.804	0.806	0.765	0.765
Revised : 30% reduction	84.3		0.824	0.697	0.778
Revised : 50% reduction	76.7		0.823	0.741	0.772

⊙ ***What is the appropriate treatment continuation criterion and how does this affect utility?***

Age at treatment initiation

- **ACD2:** Model start age of 50.1 years - this is older than seen in clinical practice
- **Company:** conducted exploratory analysis using the median age of the trial population (52 years), rather than the mean age (50.1 years)
- **ERG:** In practice, population age in lower – ERG explored the impact of lower ages, on next slide, at treatment start with different continuation criteria and at lower start age (ages 40 and 45 years) ICER increased **(see results later)**

⊙ ***Should the model's age at initiation be lower and reflect NHS practice?***

Summary of company's revised base case

Assumption	Type of change	ACD2 preference	Company's assumption
Duration of the disutility caused by exacerbation	Alternative assumption	Use MENSA mean durations of exacerbations	Use midpoint between Lloyd and MENSA
Treatment-dependent utilities baseline not adjusted	Alternative assumption	No utility gain obtained for mepolizumab treatment on top of exacerbation reduction	Different utilities based on DREAM for on and off treatment
Age-adjustment of utilities	Alternative assumption	Yes	No
EQ-5D baseline adjusted	New evidence	Unadjusted	Baseline adjusted
Asthma-related mortality	New evidence	Combination of Watson et al and Roberts et al	Results from company's new observational study

Results of company's revised base case – ICER (£/QALY)

Results	Company's revised ICER (£/QALY) Mepo vs SoC
Original Continuation Criterion	£31,724
Revised Continuation Criteria, 50% Reduction	£27,418
Revised Continuation Criteria, 30% Reduction	£28,398
Continuation criteria which includes a reduction to dose of maintenance oral corticosteroids	
Revised Continuation Criteria, 50% Reduction, including corticosteroid benefit	£18,418 to £23,418
Revised Continuation Criteria, 30% Reduction, including corticosteroid benefit	£19,398 to £24,398

ERG's revised scenario analyses

Scenario ICER based on AC's preferred base case)

1. New rates for asthma-related mortality (£50,941)
2. Percentage of patients meeting continuation based on patients who continued in COSMOS (£48,956)
3. Mean age of accepted population (51.5 years) (£44,304)
4. Attrition rate of patients in the accepted population that met the continuation rates in MENSA and continued in COSMOS (£49,124)
5. Duration of disutility of exacerbations: midpoint between MENSA and Lloyd et al.(£46,206)
6. Treatment dependent EQ-5D (baseline adjusted) (£32,670)
7. Treatment dependent EQ-5D (not adjusted for baseline imbalance) (£40,704)

Company and ERG revised ICERS
mepolizumab vs SoC

	Company's base case	AC's preferred base case + new evidence (scenarios 1-4)	ERG's most plausible base case**
Original continuation criteria	£32,235*	£48,084	£31,895
Revised continuation criteria: 30% exacerbation reduction	£28,398	£49,376	£31,378
Revised continuation criteria: 50% exacerbation reduction	£27,418	£45,831	£29,163

*Based on the amended percentage of patients meeting CC, as explained in the ERG critique

** based on revised ERG scenarios 1-6 & ERG utility adjustment

ERG's sensitivity analysis: age at treatment start on the ICER of mepolizumab versus SoC for different continuation criteria

	ACD2 preferred base case + new evidence (scenarios 1-4)			ERG's most plausible base case		
Age years	40	45	51.5*	40	45	51.5*
No worsening	£88,281	£59,271	£48,084	£44,298	£35,988	£31,895
30% reduction	£93,662	£61,271	£49,376	£42,750	£34,927	£31,378
50% reduction	£86,751	£56,965	£45,831	£39,761	£32,557	£29,163
***Base case**						

ERG data relating to waning effect

Results of the sensitivity analysis on waning effect on the ICER of mepolizumab versus SoC

	ACD2 preferred base case + new evidence (scenarios 1-4)				ERG's most plausible base case			
Treatment effect duration (years)	10	20	30	No waning*	10	20	30	No waning*
Original continuation criteria	84,811	69,497	61,651	48,084	44,582	39,995	37,419	31,895
30% reduction	95,343	74,133	64,767	49,376	46,784	39,817	37,081	31,378
50% reduction	92,068	70,381	61,042	45,831	43,429	37,392	34,744	29,163
***Base case**								

Issues for discussion

1. Population: appropriate?
2. Comparator: Has the committee heard anything to change its decision on omalizumab as a comparator?
3. Modelling: Is company's duration of an 'exacerbation' valid?
4. Utility: Does mepolizumab increase HRQoL over and above reducing exacerbations?
5. Is company's choice of way to adjust baseline EQ-5D appropriate?
6. How should utility be adjusted by age, using company data or in line with ACD2 consideration?
7. Should age at starting mepolizumab be lower and reflect the NHS?
8. What is the appropriate criteria for continuing treatment and how does this affect utility?

Back up slides

Company analysis relating to effect of mepolizumb on HRQoL (1)

- Baseline ACQ-5 and SGRQ scores, for accepted population, MENSA

		Placebo	Mepo 75mg IV/100mg SC
Baseline ACQ-5 Mean Score	N	68	171
	Mean (SD)	2.5 (1.30)	2.3 (1.25)
	Median (Min, Max)	2.5 (0, 6)	2.4 (0, 5)
Baseline SGRQ Total Score	N	68	174
	Mean (SD)	51.7 (19.46)	49.9 (18.41)
	Median (Min, Max)	52.6 (15, 95)	51.3 (5, 90)

ACQ-5: asthma control questionnaire; SGRQ: St George's Respiratory Questionnaire

Company analysis relating to effect of mepolizumb on HRQoL (2)

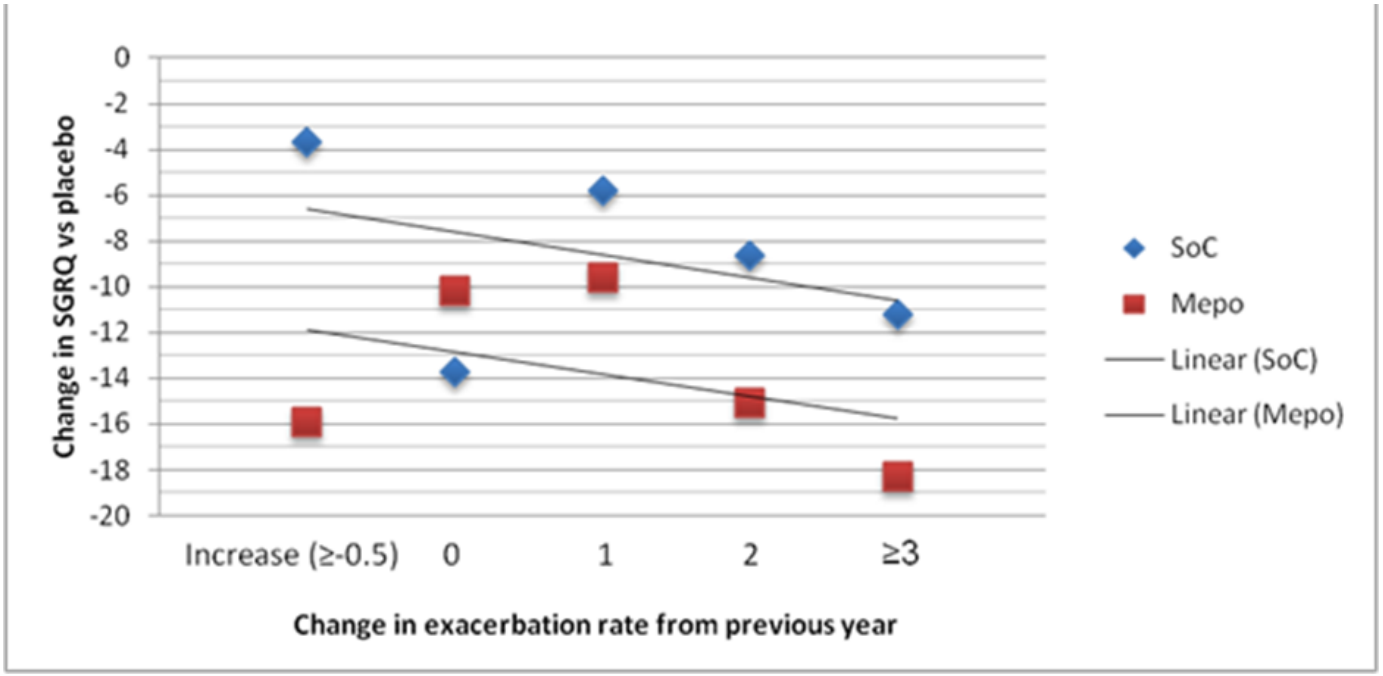
Change in ACQ-5 and SGRQ scores at 32 weeks, for accepted population, MENSA

		Placebo	Mepo 100mg SC	Mepo 75mg IV
ACQ	N	62	88	69
	LS Mean (SE)	1.97 (0.114)	1.32 (0.097)	1.4 (0.108)
	LS Mean Change (SE)	-0.37 (0.114)	-1.02 (0.097)	-0.94 (0.108)
Comparison vs placebo	Difference		-0.65	-0.57
	95% CI		-0.95, -0.36	-0.88, -0.26
	p value		<0.001	<0.001
SGRQ	N	64	91	73
	LS Mean (SE)	40.9 (2.04)	33.2 (1.71)	33.3 (1.92)
	LS Mean Change (SE)	-9.4 (2.04)	-17.1 (1.71)	-17.0 (1.92)
Comparison vs placebo	Difference		-7.7	-7.6
	95% CI		-13, -2.5	-13.2, -2.1
	p value		0.004	0.007

ACQ-5: asthma control questionnaire; SGRQ: St George's Respiratory Questionnaire

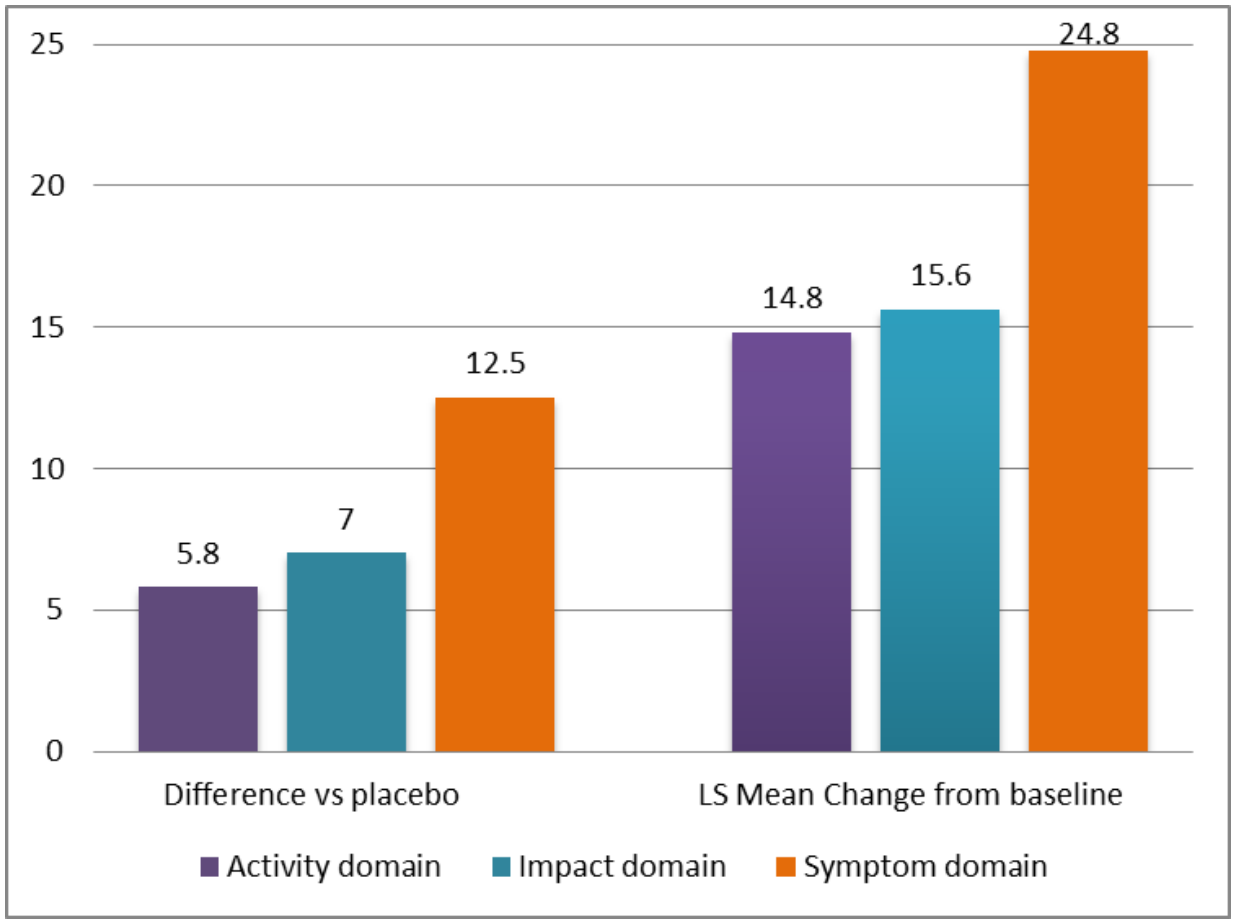
Company analysis relating to effect of mepolizumb on HRQoL (3)

Change from baseline SGRQ by absolute reduction in exacerbations compared to previous year (100mg SC & 75mg IV combined, ITT MENSA)



Company analysis relating to effect of mepolizumb on HRQoL (4)

Analysis of difference versus placebo in SGRQ score by domain versus placebo and from baseline (accepted sub-population, 100mg SC, MENSA)



Company analysis relating to effect of mepolizumb on HRQoL (5)

Analysis of Change From Baseline in SGRQ Score by Domain (accepted sub-population, MENSA)

		Placebo	100mg SC	75mg IV
Activity domain	n	64	91	74
	LS Mean (SE)	50.9 (2.58)	45.2 (2.17)	45.3 (2.41)
	LS Mean Change (SE)	-9.1 (2.58)	-14.8 (2.17)	-14.7 (2.41)
	Diff vs placebo (95 CI)		-5.8 (-12.4,0.9)	-5.6 (-12.6,1.4)
Impact domain	n	64	92	74
	LS Mean (SE)	31.9 (2.07)	24.9 (1.74)	24.0 (1.94)
	LS Mean Change (SE)	-8.6 (2.07)	-15.6 (1.74)	-16.4 (1.94)
	Diff vs placebo (95 CI)		-7.0 (-12.3,-1.7)	-7.8 (-13.5,-2.2)
Symptom domain	n	64	92	74
	LS Mean (SE)	51.3 (2.89)	38.8 (2.41)	40.2 (2.70)
	LS Mean Change (SE)	-12.3 (2.89)	-24.8 (2.41)	-23.5 (2.70)
	Diff vs placebo (95 CI)		-12.5 (-19.9,-5.1)	-11.2 (-19,-3.4)

SGRQ: St George's Respiratory Questionnaire; CI: 95% confidence interval; SE: standard error

Company analysis relating to age adjusted utility

Analysis of age on EQ-5D, observed and baseline adjusted values in DREAM ITT, SoC group, mean (SE)

	Observed		Baseline Adjusted	
Age category	Pre week 16	Post week 16	Pre week 16	Post week 16
25-35	0.835 (0.061)	0.725 (0.131)	0.764 (0.032)	0.767 (0.026)
35-45	0.716 (0.084)	0.756 (0.092)	0.763 (0.028)	0.767(0.021)
45-55	0.807 (0.038)	0.791 (0.043)	0.763 (0.026)	0.766 (0.020)
55-65	0.803 (0.037)	0.800 (0.044)	0.763 (0.028)	0.766 (0.022)
≥65	1 (n/a*)	0.922 (n/a*)	0.762 (0.033)	0.765 (0.026)
***n=1 so no SE**				

Company data relating to continuation criteria (1)

Summary of subjects in the accepted subgroup treated with mepolizumab meeting and not meeting a 50% (or 30%) reduction in exacerbations in MENSA and COSMOS, compared to the baseline exacerbation rate the year prior to MENSA

	MENSA		COSMOS	
Continuation criteria	Met / not met percentage reduction in exacerbations at end of MENSA, n (% of total population, n=159) (Continuation criteria)		Met / not met percentage reduction in exacerbations at end of COSMOS, n (% of total population, n=159)(post continuation criteria)	
			Met	Not met
≥50% reduction in exacerbation rate vs. baseline	Total n	159	121 (76)	38 (24)
	Met	122 (77)	103 (65)	19 (12)
	Not met	37 (23)	18 (11)	19 (12)
≥30% reduction in exacerbation rate vs. baseline	Total n	159	136 (86)	23 (14)
	Met	134(84)	124 (78)	10 (6)
	Not met	25 (16)	12 (8)	13 (8)

Percentages in rows and columns are in relation to the total number of subjects (N=159)

Model inputs for continuation criteria

Variable		Mean	SE	Source
Exacerbation parameters				
Patients meeting mepolizumab continuation criteria				
No reduction	Rate	1.020	0.114	COSMOS from MENSA
50% reduction	Rate	0.890	0.132	COSMOS from MENSA
30% reduction	Rate	1.020	0.124	COSMOS from MENSA
Not meeting continuation criteria				
No reduction	Rate	5.260	0.248	COSMOS from MENSA
50% reduction	Rate	3.270	0.182	COSMOS from MENSA
30% reduction	Rate	3.720	0.225	COSMOS from MENSA
% patients meeting mepo continuation criteria				
No reduction	p%	0.892	0.023	MENSA
50% reduction	p%	0.767	0.034	MENSA
30% reduction	p%	0.843	0.029	MENSA
Utilities Meeting Continuation criteria				
No reduction	Utility	0.806	0.023	DREAM
50% reduction	Utility	0.823	0.023	DREAM
30% reduction	Utility	0.824	0.023	DREAM

SE: standard error

Summary of effect on the company's ICERs for each change

Assumption in ACD	ACD2 preferred assumption	Revised company base case	One way impact on the ICER from committee preferred to revised company base case
Age: Model start age is 50.1	Not in ACD2 base case	✔	N/A
Treatment duration: Lifetime	✔	✔	N/A
Exacerbations rates: Source of exacerbation rates ERG & committee's preference	✔	✔	N/A
Duration of exacerbation: Taken from MENSA relating to resource use	✖	Not in base case Used midpoint	-£2,012
Effect on symptoms: No effect obtained on top of exacerbations	✔	Not in base case used EQ-5D	-£7,644
EQ-5D Preferred to SGRQ	✔	Not in base case used adjusted EQ-5D	-£11,314*
Age adjusted utility	✔	Not in base case No adjustment	-£1,350
Age adjusted mortality	✔	New evidence	+£1,164

Company's revised scenario analyses

- Four scenario analyses are presented to explore the uncertainties around the ERG and the company base case, assuming the original continuation criteria, and a 50% and 30% continuation criteria.

1. Using duration of exacerbations from MENSA rather than the midpoint of Lloyd and MENSA
2. Turning on the utility age adjustment, rather than being off
3. Applying the EQ-5D mapped from SGRQ values, to indicate the potential scale of the ceiling effect
4. Using the median age of the trial population (52 years), rather than the mean age (50.1 years)

ICERs depending on assumptions were between:

£21,275 and £28,134 (50% ↓ in exacerbations)

£23,193 and £29,828 (30% ↓ in exacerbations)